CME review article

This educational activity is supported by an educational grant from GlaxoSmithKline

Oral allergy syndrome: a clinical, diagnostic, and therapeutic challenge

Christopher M. Webber, MD,* and Ronald W. England, MD*

Objectives: To provide a review of the literature and discuss the clinical, pathophysiologic, diagnostic, and therapeutic challenges of oral allergy syndrome (OAS).

Data Sources: English-language publications on OAS (and pollen-food allergy syndrome) were identified through MEDLINE and through the reference lists of each identified article and review.

Study Selection: Articles pertaining to OAS with respect to its varied clinical presentation, underlying pathophysiology, available and investigational diagnostic testing, and evidence-based treatment options were selected.

Results: OAS occurs in patients with a prior cross-reactive aeroallergen sensitization and clinically presents with initial oral-pharyngeal symptoms after ingestion of a triggering fruit or vegetable. Although controversial, these symptoms may progress to systemic symptoms outside the gastrointestinal tract in 8.7% of patients and anaphylactic shock in 1.7%. OAS's underlying pathophysiology may play a role in clinical presentation and outcome, depending on whether the cross-reactive protein is a heat-labile PR-10 protein, a partially labile profilin, or a relatively heat-stable lipid transfer protein. Diagnostic testing is variable based on the underlying food tested, but fresh food skin prick test typically has the highest sensitivity. Treatment centers on avoidance and the consideration of self-injectable epinephrine. Because of its relationship with a cross-reactive aeroallergen sensitization, subcutaneous immunotherapy and sublingual immunotherapy have also been therapeutically tried with mixed results.

Conclusion: OAS is a challenging diagnosis to the practicing allergist because of its many clinical, diagnostic, and therapeutic considerations. Understanding these challenges and their underlying mechanisms can facilitate a knowledgeable approach to treating an oral allergy patient.

Ann Allergy Asthma Immunol. 2010;104:101–108.

Off-label disclosure: Drs Webber and England have indicated that this article does not include the discussion of unapproved/investigative use of a commercial product/device.

Financial disclosure: Drs Webber and England have indicated that in the last 12 months they have not had any financial relationship, affiliation, or arrangement with any corporate sponsors or commercial entities that provide financial support, education grants, honoraria, or research support or involvement as a consultant, speaker's bureau member, or major stock shareholder whose products are prominently featured either in this article or with the groups who provide general financial support for this CME program.

Instructions for CME credit

1. Read the CME review article in this issue carefully and complete the activity by answering the self-assessment examination questions on the form on page 109.
2. To receive CME credit, complete the entire form and submit it to the ACAAI office within 1 year after receipt of this issue of the *Annals*.

INTRODUCTION

Oral allergy syndrome (OAS) has been clinically recognized as a unique presentation of food allergy for more than 70 years. Despite its longevity in the literature, OAS remains a significant diagnostic and therapeutic challenge to both practicing and research allergists. This difficulty stems from the syndrome's conflicting definitions, unique underlying pathophysiology, variable diagnostic test accuracy, and limited treatment modalities. This review discusses these challenges and the evolution of OAS. English-language publications on OAS (and pollen-food allergy syndrome) were identified through MEDLINE and through the reference lists of each identified article and review. Articles pertaining to OAS with respect to its varied clinical presentation, underlying patho-

Affiliations: * Department of Allergy and Immunology, Wilford Hall Medical Center, Lackland Air Force Base, San Antonio, Texas.

Disclaimer: The opinions or assertions herein are the private views of the authors and are not to be construed as reflecting the views of the US Department of the Air Force or the US Department of Defense.

Received for publication July 30, 2009; Received in revised form August 14, 2009; Accepted for publication August 17, 2009.

doi:10.1016/j.anai.2009.11.007

physiology, available and investigational diagnostic testing, and evidence-based treatment options were selected.

OAS has been a challenging diagnosis since the first published article in 1942 in which Tuft and Blumstein[1] discussed clinical observations of 4 adult patients who presented with itching of the soft palate and swelling of mucous membranes after eating various raw fruits. All patients reported a clinical history of "hay fever" and indicated that their oral symptoms had a greater incidence during the summer months when seasonal allergies were worse. In addition, these patients reported that cooked, canned, and preserved forms did not cause symptoms. Tuft and Blumstein recognized this as a unique phase of food allergy in 1936 but had difficulty establishing its immunologic correlation. This connection came 6 years later with their inventive use of freshly extracted fruit juices in skin prick testing (SPT), which yielded positive reactions. These findings were eventually published. Interestingly, this article's commentary revealed the publication to be more remarkable for a positive SPT result using fresh fruit extract in the setting of a previously negative test result and not for the first case presentation of OAS.

Today OAS is recognized as a worldwide problem and may represent the most common food allergy in adults. This speculation is largely because of its relationship with allergic rhinitis, which affects 10% to 30% of adults and up to 40% of children.[2] However, a true prevalence of OAS has yet to be determined. Early investigations described OAS prevalence based on specific fruits involved and their correlation with aeroallergens, such as the 1970 survey by Anderson et al[3] that asked 2,067 patients about symptomatic oral pruritus to either generalized or specific fruits, namely, melon and banana. Their results showed 4.3% of all patients interviewed and 6.2% of those with pollinosis described OAS symptoms. All these patients also demonstrated clinical and SPT reactivity to ragweed. A more comprehensive study was performed in 1982 by Eriksson et al,[4] who questioned 600 adult and pediatric patients with documented allergic rhinitis (positive SPT or radioallergosorbent test [RAST] test results) regarding their tolerance of various foods. The results of this study found oral allergy symptoms in 70% of birch allergic individuals but only 20% of patients allergic to grass and mugwort. These studies remain today's foundation for estimating OAS prevalence. However, allergists answering the 2003 survey by Ma et al[5] on their management of OAS estimated the syndrome's prevalence to be 5% in children and 8% in adult patients with nonspecific pollen allergies. In their discussion, the authors cited both physician underdiagnosis and patient underreporting to explain their lower prevalence compared with earlier research.[5] There have not been any comprehensive studies specifically designed to determine a true prevalence of OAS.

DEFINITION

It is possible, however, that a true prevalence cannot be performed at this time because of recent controversy about the very definition of OAS. The earliest descriptive studies recognized a unique presentation of food allergy with oral-pharyngeal symptoms provoked by exposure to specific food allergens. Typical symptoms are isolated to the oral-pharyngeal mucosa and commonly include itching and tingling of the lips, mouth, and throat but may also include swelling or angioedema of the tongue.[1]

In 1987, Amlot et al[6] published a comprehensive description of symptoms due to IgE-mediated food hypersensitivity in 80 patients with either atopic eczema or atopic reactivity to foods. In this study, Amlot et al noted one subgroup of patients in whom approximately half described only typical oral symptoms and the other half described initial oral symptoms that chronologically progressed to include gastrointestinal manifestations (nausea, vomiting, diarrhea, and abdominal pain), then urticaria or angioedema, and rarely more severe symptoms of anaphylaxis.[6] To capture this entire group's pattern of initial oral-pharyngeal symptoms and including those with a chronologically ordered symptom progression, Amlot et al coined the actual term *oral allergy syndrome*, which we continue to use today.

During the last 15 years this definition has been challenged. Some authors contend that OAS should be strictly confined to the oral cavity and any extraoral or systemic symptoms should result in a diagnosis of food anaphylaxis.[7,8] Their definition is derived from patient care scenarios in which misdiagnosis of OAS may result in inadequate treatment of potentially life-threatening food anaphylaxis. This concern is supported by the survey of Ma et al[5] on allergist's management of OAS, which found 13% of allergists gave a misdiagnosis of OAS to a child with peanut allergy and that 25% did not consider prescribing epinephrine. This survey also found that 20% of allergists applied the term *OAS* to a patient with systemic symptoms caused by fruit.

Regardless of the final definition, today's allergists need some form of risk evaluation to guide patient education and treatment. In 1993, Ortolani et al[9] conducted a review of OAS studies to create a "summary of symptoms elicited in allergic subjects by eating fruits and vegetables." On the basis of this review and as mathematically aggregated in the survey by Ma et al,[5] in addition to the typical oral-pharyngeal symptoms, 8.7% of patients experience systemic symptoms outside the gastrointestinal tract, 3% experience systemic symptoms without oral symptoms, and 1.7% experience anaphylactic shock. Although these numbers may temporarily help guide patient care decisions, dedicated research is needed to adequately answer the incidence of symptoms outside the oral cavity and whether risk factors can be identified.

IMMUNOLOGIC MECHANISM

Any controversy in OAS's definition will likely be restricted to its varied clinical presentation because the current understanding of OAS's underlying pathophysiology supports the outcomes of both isolated oral symptoms and anaphylaxis. This is in part due to multiple different types of antigens capable of causing oral allergy symptoms and the unique nature of the antigens themselves. However, before these

antigens could be identified, OAS's relationship to pollinosis had to be established.

It was not until the late 1970s, when Andersen et al used the crossed-line immunoelectrophoresis technique, that the first antigenic correlation among birch, apple, potato, and hazelnut was realized.[10] After confirming an immunologic identity between birch and hazelnut, the authors also recognized a shared "affinity precipitate" between birch and both apple and potato, which they speculated might be an extremely labile allergen or possibly a plant lectin. In 1999, Kazemi-Shirazi et al[11] advanced this theory by combining multiple food and pollen antigens in quantitative RAST and immunoblot inhibition assays. They identified that food specific IgE epitopes in OAS patients resembled pollen antigens. As a result they concluded that the pollen allergens themselves may be responsible for the elicitation and maintenance of oral allergy symptoms, tying together the longstanding clinical correlation through cross-reactive allergens.

Today we recognize that OAS is caused by an IgE cross-reactivity between a prior aeroallergen sensitization and a characteristically difficult to extract and highly labile plant-derived protein.[12] This mechanism of food allergy (now called a class 2 food allergy) is unique compared with the traditional class 1 food allergy in which the sensitization process occurs through the gastrointestinal tract from a protein allergen resistant to gastric digestion. Of the different antigen groups responsible for causing OAS, perhaps the largest and most classic group is the pathogenesis-related or pathogen response (PR) proteins.

PR proteins are naturally formed in higher-order plants as responses to fungal or bacterial infections or to various stresses, such as drought, flooding, freezing temperatures, UV-B light, ozone, and mechanical injury.[13] Although biologically serving to help protect these plants against their respective environmental stimuli, in humans PR proteins become clinically relevant when an IgE antibody against 1 PR protein, such as an aeroallergen, cross-reacts with a similar PR protein from a different plant or food source, resulting in oral allergy symptoms. The largest group of PR proteins causing OAS comes from the PR-10 family.

A key member of the PR-10 family of PR proteins is the major birch tree allergen, *Betula verrucosa* (Bet v) 1. Sensitization to this aeroallergen can result in cross-reactivity to homologous proteins in many foods, including members of the Rosaceae fruits (eg, apple [Mal d 1], cherry [Pru av 1], apricot [Pru ar 1], pear [Pyr c 1]), the Apiaceae vegetables (eg, carrots [Dau c 1], celery [Api g 1]), and potato (pSTH) and hazelnut (Cor a 1) (Table 1).[12] Although Bet v 1 may be a stable aeroallergen, the PR-10 (or Bet v 1–type) proteins are unstable to both heating and digestion. This feature explains early researchers' difficulty isolating the proteins and OAS's tendency toward oral-pharyngeal symptoms that rapidly resolve without progression to systemic symptoms because the underlying antigen is denatured and destroyed during digestion.[14]

Although the PR-10 family of PR proteins is the largest contributor to OAS, not all patients with OAS are sensitized to birch and not all causative foods contain Bet v 1–type proteins. Attempts to reconcile this difference have resulted in the identification of additional proteins causing OAS. The PR-5 family of thaumatin-like proteins has been identified with in vitro cross-reactivity between mountain cedar's Jun a 3 allergen and cherry (Pru av 2), apple (Mal d 2), and paprika or bell pepper (P23).[13] Another cause of OAS was uncovered when Valenta et al[15] cloned and identified a novel birch antigen, Bet v 2. This antigen, however, was found in patients with and without birch allergy and led to the realization of a larger, non–PR-related protein family capable of causing oral allergy symptoms: the profilins.

Profilins are 12- to 15-kDa, monomeric, actin-binding proteins found in eukaryotic cells and probably function to mediate membrane-cytoskeleton interaction.[14,16] As such, they are ubiquitous across a broad range of inhalant and nutritive allergen sources, leading to cross-reactivity and OAS symptoms without birch sensitization.[14] Profilin is involved in the celery-mugwort-spice syndrome and has other homologous proteins in apple, pear (Pyr c 4), carrot (Dau c 4), celery (Api g 4), potato, and tomato.[12,17] Similar to PR-10 proteins, profilins are generally considered to be labile and easily degraded by gastric digestion, resulting in typical oral allergy symptoms.[18] However, there has been a partially heat-stabile profilin identified in a profilin-mediated systemic reaction to zucchini and a report of a profilin-mediated anaphylactic reaction to lychee fruit.[19,20]

Although cross-reactivity within the PR-10 or profilin families causes OAS, the lability of these proteins should limit their potential to cause systemic reactions. However, systemic reactions can occur. Addressing this discrepancy, studies analyzing OAS patients with frequent systemic symptoms revealed a novel 9- to 10-kDa OAS-causing pan-allergen: the lipid transfer protein (LTP).[21,22] LTPs function to transfer phospholipids from liposomes to mitochondria but also help plant defense as an antifungal and antibacterial agent, resulting in their current classification as the PR-14 protein family.[12] Because of LTP's 3-dimensional structure rich in α-helices and cysteine residues, these proteins are stable to thermal processing and proteolysis.[14] As a result, LTPs can cause both OAS and traditional class 1 food anaphylaxis.[23,24] LTPs are most often clinically found as pan-allergens in the Rosaceae family (eg, peach [Pru p 3], apricot [Pru ar 3], plum, and cherry) but are also found in apple (Mal d 3), tomato, carrot, barley, corn, wheat, rice, sorghum, broccoli, onion, and grapevine.[12,13,17,23,25]

The protein differences between the heat and proteolysis stable LTPs and the more labile PR-10 and profilin proteins can be used to explain both the subset of anaphylactic individuals according to the OAS definition of Amloet et al and justification to separate OAS's oral-pharyngeal symptoms from extraoral food anaphylaxis.[6] Ironically, these studies themselves are complicated by inclusion criteria based on differing definitions of OAS, which limits the utility of any

Table 1. Common OAS Triggers and Related Allergens and Source

Food	Allergen and source							
	Trees			Grass nonspecific	Weeds			No pollen
	Birch	Cedar	Ficus		Mugwort	Ragweed	Goosefoot	
Aniseed					Unknown[17a]			
Apple	PR-10[12]	PR-5[13b]						LTP[13]
Apricot	PR-10[12]							LTP[12]
Asparagus								LTP[25]
Banana						Profilin[17]	Profilin[17]	
Bell pepper		PR-5[13b]						
Broccoli					Unknown[17a]			
Cantaloupe					Unknown[17a]	Unknown[17a]		
Caraway seed					Unknown[17a]			
Carrot	PR-10[12]			Profilin[12]	Profilin[17]			
Cauliflower					Unknown[17a]			
Celery	PR-10[12]			Profilin[12]	Profilin[12]			
Chamomile					Unknown[17a]			
Cherry	PR-10[12]	PR-5[13b]						LTP[12]
Chicory	PR-10[25]							
Coriander					Unknown[17a]			
Fennel					Unknown[17a]			
Fig	Unknown[24a]		Unknown[25a]	Unknown[25a]				
Garlic							Profilin[17]	
Hazelnut	PR-10[13]							LTP[25]
Honeydew						Unknown[17a]		
Jackfruit	PR-10[25]							
Kiwi fruit		PR-5[13]						
Leek					Unknown[17a]			
Lettuce								LTP[25]
Lychee								Profilin[19]
Maize								LTP[13b]
Mango					Unknown[17a]			
Melon						Profilin[17]	Profilin[17]	
Mustard					Profilin[17]			
Onion					Unknown[17a]			
Paprika		PR-5[13b]			Unknown[17a]			
Parsley	PR-10[12]				Unknown[17a]			
Peach	PR-10[13]				Profilin[17]		Profilin[17]	LTP[12]
Peanut	PR-10[25]							
Pear	PR-10[12]							
Potato	PR-10[12]							
Plum	PR-10[12]							
Soybean								LTP[12]
Tomato		PR-5[13]						
Watermelon						Unknown[17a]		
Zucchini						Profilin[17]		

Abbreviations: LTP, lipid transfer protein; OAS, oral allergy syndrome; PR, pathogen response.
[a] Although a clinical relationship has been described, the exact protein class is not established.
[b] In vitro sequence homology between pollen and fruit; no reported in vivo reactions.

pathophysiology-based distinction of OAS's ultimate definition.

DIAGNOSIS

In addition to its clinical and immunologic complexities, OAS has also been a diagnostic challenge since its initial case report, which took 6 additional years and the creation of a novel diagnostic technique to prove sensitization by skin testing.[1] Today's diagnostic testing continues to vary in sensitivity and specificity, largely as a result of OAS's multiple causative antigens and their potential lability. However, before reviewing individual test results, the first challenge in diagnosing OAS is to establish the "gold standard" of true disease.

The double-blinded, placebo-controlled food challenge (DBPCFC) is widely accepted as the "gold standard" for diagnosing traditional food allergy and many would agree for diagnosing OAS as well.[26] In a study comparing OAS history to DBPCFC, Rodriguez et al[27] demonstrated that of 53 patients with a history of OAS to melon, only 25 had a positive open food challenge (OFC) result, and of those, only 17 had positive DBPCFC results. Considering these results, many diagnostic tests have been compared with DBPCFC as the standard to reflect true disease.

However, some authors challenge this "gold standard," advocating that a careful clinical history is sufficient to diagnose OAS and may better reflect true disease.[28,29] This argument is based on OAS's unique clinical symptoms and the potential that some blinding processes may not guarantee oral contact with enough provoking antigen due to OAS's antigenic lability.[28] Supporting this idea, Anhoej et al[30] found that a good clinical history of OAS to apple had negative and positive predictive values of 100% and 92% when compared with OFC, respectively. As a result, some studies compare the sensitivity and specificity of diagnostic testing using clinical history as the "gold standard." Both considerations are reviewed herein.

COMMERCIAL AND FRESH FRUIT SPTS

When considered collectively, both the commercial SPT (CSPT) and the fresh fruit skin prick test (FFSPT) are highly variable based on the underlying food being tested (Table 2). Between the 2, many authors have debated the reliability of the CSPT, which has yielded sensitivities ranging from 87.5% for potato to 0% for pear.[28] This wide variation may be due to inadvertent denaturation of the OAS antigens, particularly the PR-10 proteins, during commercial processing.[31,32]

Comparing CSPT with FFSPT using clinical history as a true-positive result, Ortolani et al[28] found that FFSPT yielded better sensitivity and specificity in diagnosing OAS. This observation was particularly relevant for allergens, such as apple, orange, tomato, carrot, celery, cherry, and peach. Similar results were reported by Osterballe et al[33] in birch allergic patients having OAS to apple, with FFSPT's sensitivity ranging from 70% to 80%, which compared with a 10% sensitivity using CSPT. In another study using OFC as the "gold standard," Anhoej et al[30] evaluated the diagnostic ability of FFSPT on 36 grass and/or birch allergic patients. They found FFSPT to hazelnut, apple, and melon had a sensitivity of 0.97, 0.92, and 0.98 and specificities of 0.78, 0.72, and 0.82, respectively.

In addition to differences among SPT methods, special consideration to the antigen being tested must also be considered in diagnosing OAS. Although most studies focused on foods related to the PR-10 protein family, Asero et al[34] in 2008 skin tested 200 consecutive pollen allergic patients to date-palm profilin and found that 35% of patients were sensitized only to profilin. In another study by Asero et al,[22] patients with OAS to peach without birch sensitization reacted to LTPs, which were more concentrated in the fruit's

Table 2. Comparison of Diagnostic Tests for Oral Allergy Syndrome

Test	Foods tested																	
	Apple		Peanut		Orange		Carrot		Tomato		Hazelnut		Pea		Celery			
	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %		
FFSPT	82[28]	65[28]	12[28]	93[28]	67[28]	73[28]	100[28]	42[28]	75[28]	61[28]	41[28]	80[28]	62[28]	50[28]	100[35]	NA		
CSPT	2[28]	100[28]	67[28]	46[28]	27[28]	97[28]	80[28]	65[28]	25[28]	79[28]	22[28]	85[28]	75[28]	40[28]	NA	NA		
RAST	70[28]	72[28]	42[28]	61[28]	20[28]	81[28]	50[28]	87[28]	31[28]	86[28]	48[28]	75[28]	50[28]	80[28]	73[35]	NA		
BAT (10% activation)	75[36]	68[36]	NA	NA	NA	NA	85[35]	85[35]	NA	NA	90[35]	90[35]	NA	NA	85[35]	80[35]		
CAST-ELISA	NA	NA	NA	NA	NA	NA	43–86[38]	77–91[38]	NA	NA	67–80[38]	75–88[38]	NA	NA	71–95[38]	92–67[38]		

Abbreviations: BAT, basophil activation test; CAST-ELISA, cellular antigen stimulation test in combination with enzyme-linked immunosorbent assay; CSPT, commercial skin prick test; FFSPT, fresh fruit skin prick test; NA, not available.

skin. Considering these results, the ability to test antigens beyond the PR-10 subgroup may help explain FFSPT's diagnostic advantage over the focused antigen of CSPT. Of note, because of the ubiquitous nature of these pan-allergens, relying on profilin or LTPs alone may result in false-positive test results and an incorrect diagnosis of OAS.[16]

SPECIFIC IgE TESTING: IMMUNOCAP AND RAST

Specific IgE testing is another method used to diagnose OAS. Similar to SPT, specific IgE testing also varies based on the underlying food. In 1988, Ortolani et al[28] directly compared SPT to Phadebas RAST in patients with a clinical history of OAS. They found the diagnostic accuracy between FFSPT and RAST was comparable for peanut, hazelnut, and pea, whereas RAST was superior in walnut. However, FFSPT remained superior for sensitivity for apple, orange, tomato, carrot, cherry, celery, and peach. A more recent study compared FFSPT with ImmunoCAP in patients with a clinical history of OAS to melons.[27] Although the 95% confidence intervals between each group overlapped, this study showed the positive predictive values of FFSPT vs ImmunoCAP were comparable at 42% and 44%, respectively. The negative predictive values were 77% for FFSPT and 70% for ImmunoCAP. As with SPT, the underlying antigen being tested should be considered.

BASOPHIL ACTIVATION TEST

A more recent test explored for its diagnostic potential in OAS is the basophil activation test (BAT). The uniqueness of IgE-activated basophils to both secrete quantifiable bioactive mediators and to exhibit CD63 makes this a potentially useful in vitro diagnostic test. In a study of 29 patients with a clinical history of OAS and using a threshold of activated basophil counts higher than 10% of the total IgE-positive basophil population, BAT was 85% sensitive for carrots and celery and 90% sensitive for hazelnut.[35] Interestingly, in this study the sensitivity of FFSPT was 100% to carrot, 100% to celery, and 90% to hazelnut. Specificities using BAT were 85% to carrot, 80% to celery, and 90% to hazelnut. In a separate study of birch allergic patients with a history of OAS to apple, BAT had a sensitivity and specificity of 100% compared with healthy controls.[36] However, when comparing birch allergic patients with OAS to those without, BAT's sensitivity and specificity decreased to 88% and 75%, respectively. A similar experiment focusing on recombinant antigens showed BAT had a sensitivity and specificity of 75% and 68% to apple, 65% and 100% to carrot, and 75% and 77% to celery, respectively.[37]

SULFIDOLEUKOTRIENE RELEASE ASSAY

Another potential technique explored for the diagnosis of OAS is the sulfidoleukotriene release assay. Combining the cellular antigen stimulation test with an enzyme-linked immunosorbent assay (CAST-ELISA), Ballmer-Weber et al[38] tested the value of basophil leukotriene release to diagnose OAS. In birch-sensitized patients with positive DBPCFC results, CAST-ELISA showed a sensitivity of 71% to 95% for celery, 73% to 80% for hazelnut, and 43% to 86% for carrot. Again, the comparable FFSPT sensitivities to celery, hazelnut, and carrot were 100%, 80%, and 100%, respectively. However, CAST-ELISA had higher specificities for OAS than CAP-FEIA IgE testing, resulting in a higher positive predictive value.

TREATMENT

As discussed in the Practice Parameters, the treatment of food allergy is avoidance, education, and emergency management with injectable epinephrine.[26] Although different from a traditional class 1 food allergy, OAS remains a food allergy and the same basic tenets of treatment may apply. However, there are 2 potential pitfalls specific to the treatment of OAS. First, there is the potential for an improper diagnosis of OAS in a patient with food anaphylaxis. The survey of Ma et al revealed 20% of allergists classified a systemic reaction to peach as OAS, whereas another 25% did not prescribe epinephrine for a systemic peach allergy manifested by initial oral-pharyngeal symptoms.[5] Second, there is the potential to dismiss the properly selected oral allergy patient as having no risk of anaphylaxis. Although this is currently a debated topic in the literature, until a comprehensive evidence-based definition of OAS can be determined, the survey of Ma et al suggests that 8.7% of OAS patients experienced systemic symptoms outside the gastrointestinal tract and 1.7% experienced anaphylactic shock.[5] For these possibilities, Ma et al report that 3% of practicing allergists will always give self-injectable epinephrine to an OAS patient, 67% prescribe epinephrine on a case-by-case basis, and 30% never prescribe epinephrine.[5] Although there is currently no therapeutic consensus, recognizing the potential pitfalls in treatment can help individualize the recommendations of avoidance, education, and emergency management to oral allergy patients.

In the traditional type 1 food allergic patient, trigger avoidance and the use of self-injectable epinephrine for reactions to unintentional exposure remain the standard therapy. However, because OAS is believed to be initiated by a primary aeroallergen sensitization, the role of immunotherapy has been reexamined as a potential therapy specific to OAS. Starting with the early positive case report of fresh fruit tolerance after a year of pollen immunotherapy reported by Kelso et al,[39] multiple studies have examined the effects of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) on OAS. The results have been mixed.

In 1995, Hermann et al[40] surveyed 20 patients with birch-pollen allergy during 2 to 3 years of SCIT and showed that in 9 of 20 (45%) oral allergy symptoms improved, although the duration of this effect was limited. In 1998, Asero et al[41] prospectively followed up 49 birch-sensitive patients with OAS to apple after receiving 1 to 3 years of birch SCIT. When compared with controls, 41 of 49 (84%) reported subjective improvement in OAS symptoms. Of these, 19 of 41 (46%) showed a 50% to 95% improvement and 22 of 41 (54%) showed complete disappearance of OAS symptoms. In

a separate study by the same author, a single patient with OAS to fennel and cucumber and laryngeal edema to melon was initiated on SCIT to grass, mugwort, and ragweed pollen.[42] After 36 months of immunotherapy, the patient tolerated an open challenge to fennel and cucumber without experiencing any symptoms, and after 43 months of SCIT she underwent an open challenge to melon without any consequence.

Additional studies have demonstrated an improvement in apple tolerance after SCIT through pretreatment and posttreatment food challenges. Bolhaar et al[43] showed that 9 of 13 patients (69%) had improved OAS visual analog scores after 12 months of SCIT and 3 of 9 (33%) had complete symptom resolution based on DBPCFC. A later study by Bucher et al[44] compared pretreatment and posttreatment OFCs on patients with OAS to apple and hazelnut after a 12-month course of birch-inclusive SCIT. At the conclusion of the study period, 13 of 15 patients (87%) could eat more apples or hazelnuts before provoking clinical symptoms, with the tolerated quantity of apple increasing from 12.6 to 32.6 g. Although this represented a statistically significant increase, the authors noted the potentially limited clinical relevance to the patient's management.[44]

Overall, these studies demonstrated some potential desensitization during active pollen immunotherapy in OAS. However, 1 study suggested questionable long-term benefit. Specifically addressing this concern, Asero[45] published a follow-up study on the duration of birch immunotherapy's effect in conferring apple tolerance. Of the initial study population, 27 of 30 patients (90%) remained apple tolerant 6 months after completing SCIT. This number decreased to only 11 of 30 patients (34%) remaining symptom free after 30 months and progressively decreased such that of the 3 patients attending the 42-month follow-up, only 2 of 30 (0.07%) remained apple tolerant. As a potential explanation for SCIT's variability to induce OAS tolerance, the same author published an editorial that suggested that higher antigen quantities may be required to induce an appreciable effect on OAS compared with those needed for pollen-related symptoms.[46]

As an alternative approach to SCIT, some authors have evaluated the effectiveness of pollen-specific SLIT in modifying oral allergy symptoms. Kinaciyan et al[47] evaluated 15 patients with apple OAS undergoing birch-pollen SLIT and demonstrated no significant change in OAS tolerance, despite 9 of 15 patients (60%) reporting subjective improvement in nasal provocation to aeroallergens. Two larger studies also examined SLIT but did so as a comparison among SLIT, SCIT, and placebo. Möller[48] enrolled 72 children with birch allergies and typical OAS symptoms to receive SCIT (n = 42), SLIT (n = 14), and placebo (n = 16) and found that neither the SCIT nor SLIT group had significantly improved food sensitivity over placebo. A recent study by Hansen et al[49] enrolled 74 birch allergic patients into a double-blind, double-dummy, placebo-controlled comparison between 2 years of SCIT and SLIT. Comparing pretreatment OFCs and posttreatment OFCs in a subgroup of 51 patients with OAS symptoms to apple, the authors noted a trend toward a decrease in clinical reactivity to plant foods in all groups, including placebo. As a result, neither SCIT nor SLIT significantly affected apple tolerance.

CONCLUSIONS

Since the first case report, OAS has been a challenging diagnosis to the practicing allergist because of its many clinical, diagnostic, and therapeutic considerations. Although these challenges may frustrate some, they also indicate a diagnosis that is actively being shaped and structured in the literature today. Despite its initially slow start more than 70 years ago, OAS will remain an interesting topic for many years to come.

REFERENCES

1. Tuft L, Blumstein G. Studies in food allergy—sensitization to fresh fruits: clinical and experimental observations. *J Allergy.* 1942;13: 574–578.
2. Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol.* 2008;122(suppl):S1–S84.
3. Anderson LB Jr, Dreyfuss EM, Logan J, Johnstone DE, Glaser J. Melon and banana sensitivity coincident with ragweed pollinosis. *J Allergy.* 1970;45:310–319.
4. Eriksson NE, Formgren H, Svenonius E. Food hypersensitivity in patients with pollen allergy. *Allergy.* 1982;37:437–443.
5. Ma S, Sicherer SH, Nowak-Wegrzyn A. A survey on the management of pollen-food allergy syndrome in allergy practices. *J Allergy Clin Immunol.* 2003;112:784–788.
6. Amlot PL, Kemeny DM, Zachary C, Parkes P, Lessof MH. Oral allergy syndrome (OAS): symptoms of IgE-mediated hypersensitivity to foods. *Clin Allergy.* 1987;17:33–42.
7. Detjen P. Oral allergy syndrome or anaphylaxis? *Ann Allergy Asthma Immunol.* 1996;77:254.
8. Kelso JM. Oral allergy syndrome? *J Allergy Clin Immunol.* 1995;96:275.
9. Ortolani C, Pastorello EA, Farioli L, et al. IgE-mediated allergy from vegetable allergens. *Ann Allergy.* 1993;71:470–476.
10. Andersen KE, Lowenstein H. An investigation of the possible immunological relationship between allergen extracts from birch pollen, hazelnut, potato and apple. *Contact Dermatitis.* 1978;4:73–79.
11. Kazemi-Shirazi L, Pauli G, Purohit A, et al. Quantitative IgE inhibition experiments with purified recombinant allergens indicate pollen-derived allergens as the sensitizing agents responsible for many forms of plant food allergy. *J Allergy Clin Immunol.* 2000;105:116–125.
12. Breiteneder H, Ebner C. Molecular and biochemical classification of plant-derived food allergens. *J Allergy Clin Immunol.* 2000;106:27–36.
13. Midoro-Horiuti T, Brooks EG, Goldblum RM. Pathogenesis-related proteins of plants as allergens. *Ann Allergy Asthma Immunol.* 2001;87: 261–271.
14. Breiteneder H, Clare Mills EN. Plant food allergens–structural and functional aspects of allergenicity. *Biotechnol Adv.* 2005;23:395–399.
15. Valenta R, Duchene M, Ebner C, et al. Profilins constitute a novel family of functional plant pan-allergens. *J Exp Med.* 1992;175:377–385.
16. Ebo DG, Hagendorens MM, Bridts CH, De Clerck LS, Stevens WJ. Sensitization to cross-reactive carbohydrate determinants and the ubiquitous protein profilin: mimickers of allergy. *Clin Exp Allergy.* 2004; 34:137–144.
17. Egger M, Mutschlechner S, Wopfner N, Gadermaier G, Briza P, Ferreira F. Pollen-food syndromes associated with weed pollinosis: an update from the molecular point of view. *Allergy.* 2006;61:461–476.
18. Lucas JS, Cochrane SA, Warner JO, Hourihane JO. The effect of digestion and pH on the allergenicity of kiwifruit proteins. *Pediatr Allergy Immunol.* 2008;19:392–398.

19. Reindl J, Anliker MD, Karamloo F, Vieths S, Wuthrich B. Allergy caused by ingestion of zucchini (*Cucurbita pepo*): characterization of allergens and cross-reactivity to pollen and other foods. *J Allergy Clin Immunol.* 2000;106:379–385.
20. Fah J, Wuthrich B, Vieths S. Anaphylactic reaction to lychee fruit: evidence for sensitization to profilin. *Clin Exp Allergy.* 1995;25: 1018–1023.
21. Pastorello EA, Farioli L, Pravettoni V, et al. The major allergen of peach (*Prunus persica*) is a lipid transfer protein. *J Allergy Clin Immunol.* 1999;103:520–526.
22. Asero R, Mistrello G, Roncarolo D, Casarini M, Falagiani P. Allergy to nonspecific lipid transfer proteins in Rosaceae: a comparative study of different in vivo diagnostic methods. *Ann Allergy Asthma Immunol.* 2001;87:68–71.
23. Asero R, Mistrello G, Roncarolo D, et al. Lipid transfer protein: a pan-allergen in plant-derived foods that is highly resistant to pepsin digestion. *Int Arch Allergy Immunol.* 2001;124:67–69.
24. Gamboa PM, Caceres O, Antepara I, et al. Two different profiles of peach allergy in the north of Spain. *Allergy.* 2007;62:408–414.
25. Mari A, Ballmer-Weber BK, Vieths S. The oral allergy syndrome: improved diagnostic and treatment methods. *Curr Opin Allergy Clin Immunol.* 2005;5:267–273.
26. Food allergy: a practice parameter. *Ann Allergy Asthma Immunol.* 2006; 96(suppl):S1–S68.
27. Rodriguez J, Crespo JF, Burks W, et al. Randomized, double-blind, crossover challenge study in 53 subjects reporting adverse reactions to melon (*Cucumis melo*). *J Allergy Clin Immunol.* 2000;106:968–972.
28. Ortolani C, Ispano M, Pastorello EA, Ansaloni R, Magri GC. Comparison of results of skin prick tests (with fresh foods and commercial food extracts) and RAST in 100 patients with oral allergy syndrome. *J Allergy Clin Immunol.* 1989;83:683–690.
29. Cadot P, Kochuyt AM, van Ree R, Ceuppens JL. Oral allergy syndrome to chicory associated with birch pollen allergy. *Int Arch Allergy Immunol.* 2003;131:19–24.
30. Anhoej C, Backer V, Nolte H. Diagnostic evaluation of grass- and birch-allergic patients with oral allergy syndrome. *Allergy.* 2001;56: 548–552.
31. Bjorksten F, Halmepuro L, Hannuksela M, Lahti A. Extraction and properties of apple allergens. *Allergy.* 1980;35:671–677.
32. Rudeschko O, Fahlbusch B, Henzgen M, et al. Investigation of the stability of apple allergen extracts. *Allergy.* 1995;50:575–580.
33. Osterballe M, Scheller R, Stahl Skov P, Andersen KE, Bindslev-Jensen C. Diagnostic value of scratch-chamber test, skin prick test, histamine release and specific IgE in birch-allergic patients with oral allergy syndrome to apple. *Allergy.* 2003;58:950–953.
34. Asero R, Monsalve R, Barber D. Profilin sensitization detected in the office by skin prick test: a study of prevalence and clinical relevance of profilin as a plant food allergen. *Clin Exp Allergy.* 2008;38:1033–1037.
35. Erdmann SM, Heussen N, Moll-Slodowy S, Merk HF, Sachs B. CD63 expression on basophils as a tool for the diagnosis of pollen-associated food allergy: sensitivity and specificity. *Clin Exp Allergy.* 2003;33: 607–614.
36. Ebo DG, Hagendorens MM, Bridts CH, Schuerwegh AJ, De Clerck LS, Stevens WJ. Flow cytometric analysis of in vitro activated basophils, specific IgE and skin tests in the diagnosis of pollen-associated food allergy. *Cytometry B Clin Cytom.* 2005;64:28–33.
37. Erdmann SM, Sachs B, Schmidt A, et al. In vitro analysis of birch-pollen-associated food allergy by use of recombinant allergens in the basophil activation test. *Int Arch Allergy Immunol.* 2005;136:230–238.
38. Ballmer-Weber BK, Weber JM, Vieths S, Wuthrich B. Predictive value of the sulfidoleukotriene release assay in oral allergy syndrome to celery, hazelnut, and carrot. *J Investig Allergol Clin Immunol.* 2008;18:93–99.
39. Kelso JM, Jones RT, Tellez R, Yunginger JW. Oral allergy syndrome successfully treated with pollen immunotherapy. *Ann Allergy Asthma Immunol.* 1995;74:391–396.
40. Herrmann D, Henzgen M, Frank E, Rudeschko O, Jager L. Effect of hyposensitization for tree pollinosis on associated apple allergy. *J Investig Allergol Clin Immunol.* 1995;5:259–267.
41. Asero R. Effects of birch pollen-specific immunotherapy on apple allergy in birch pollen-hypersensitive patients. *Clin Exp Allergy.* 1998;28: 1368–1373.
42. Asero R. Fennel, cucumber, and melon allergy successfully treated with pollen-specific injection immunotherapy. *Ann Allergy Asthma Immunol.* 2000;84:460–462.
43. Bolhaar ST, Tiemessen MM, Zuidmeer L, et al. Efficacy of birch-pollen immunotherapy on cross-reactive food allergy confirmed by skin tests and double-blind food challenges. *Clin Exp Allergy.* 2004;34:761–769.
44. Bucher X, Pichler WJ, Dahinden CA, Helbling A. Effect of tree pollen specific, subcutaneous immunotherapy on the oral allergy syndrome to apple and hazelnut. *Allergy.* 2004;59:1272–1276.
45. Asero R. How long does the effect of birch pollen injection SIT on apple allergy last? *Allergy.* 2003;58:435–438.
46. Asero R. Effects of birch pollen SIT on apple allergy: a matter of dosage? *Allergy.* 2004;59:1269–1271.
47. Kinaciyan T, Jahn-Schmid B, Radakovics A, et al. Successful sublingual immunotherapy with birch pollen has limited effects on concomitant food allergy to apple and the immune response to the Bet v 1 homolog Mal d 1. *J Allergy Clin Immunol.* 2007;119:937–943.
48. Möller C. Effect of pollen immunotherapy on food hypersensitivity in children with birch pollinosis. *Ann Allergy.* 1989;62:343–345.
49. Hansen KS, Khinchi MS, Skov PS, Bindslev-Jensen C, Poulsen LK, Malling HJ. Food allergy to apple and specific immunotherapy with birch pollen. *Mol Nutr Food Res.* 2004;48:441–448.

Requests for reprints should be addressed to:
Christopher M. Webber, MD
Department of Allergy and Immunology
Wilford Hall Medical Center
2200 Bergquist Dr
Suite 1
Lackland Air Force Base
San Antonio, TX 78236
E-mail: Christopher.M.Webber@gmail.com